REVIEW: FRUITS OF *MORINDA CITRIFOLIA*

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ABSTRACT

This review was conducted to investigate the phytochemistry and pharmacological properties of *Morinda citrifolia*. The study was carried out by searching for keywords *Morinda citrifolia* L, noni, phytochemical Components and biological activity in different scientific articles and books published in various search engines like PubMed, science direct etc. *M. citrifolia* is commonly known as Indian mulberry, Chessy fruit or Noni in India.. *M. citrifolia* has a wide range of therapeutical uses such as arthritis, burns, headache, wounds and skin infections. The parts including fruits, seeds, barks, leaves, and flowers has their own individual nutritional and therapeutical values. However, the fruits of noni has been considered as the most important part which contain more number of chemical compounds. The major phytochemical components found to be phenolic compounds, anthraquinones, organic acids, beta-carotenoids, terpenoids, alkaloids, non-volatile and volatile components.

KEY WORDS: *Morinda citrifolia* L, Phytochemical Components, Biological Activity.

INTRODUCTION:

Ancient Ayurvedic texts cite Noni as Ashyuka, which in Sanskrit means 'longevity'. *Morinda citrifolia*, had been used as a food supplement and health enhancer, commonly known as Noni or Indian mulberry. Ancient Polynesians used raw noni fruit, internally and externally, to maintain good health and heal a variety of ailments. It has been reported that *Morinda citrifolia* has a wide range of therapeutic uses in ailments such as arthritis, burns, headache, wounds and skin infections¹. In the European Union, after safety testing on one particular brand of noni juice (Tahitian Noni), approval was granted in 2002 as a novel food by the European Commission for Health and Consumer Protection Directorate-General². *Morinda citrifolia* known as Indian Mulberry or Noni which belonging to the family Rubiaceae. Mainly these species are cultivated in the tropical regions of Southeast Asia and Australasia. Interestingly, there are around 100 names of this fruit around different regions in the world.

HISTORY

The history of this small little green fruit dates back to the ancient era of Ayurveda. Various books has reported the health benefits of noni. Australasia, South East & Southern part of Asia and Pacific islands are some parts of the world which uses noni as health enhancer. As per a few ancient manuscripts, noni fruit is loaded with natural healing agents, which can easily cure various diseases with regular consumption in the right proportions. Even after so many years, this fruit has been used to treat and prevent various health problems.

Biological source:-Noni is the fruit, leaves, bark, roots and the whole tree of *morinda citrifolia* belonging to the family Rubiaceae.

LIFE CYCLE OF NONI FRUIT:-

Other features: -Noni is a small tree which grows around 10 to 30 feet in height. It has bright green, thick, deeply veined and elliptical leaves. It has fruits with unusual shapes and about 3 to 5 inches in length and 10 to 18cm in size and ovoid. Fruit contains lots of seeds. The tree has flowers and fruits throughout the year. The immature fruit is hard in nature with dark green color and later it turns to light yellow to white as it ripens. And when ripens, it has an unpleasant odor and become tender at maturity. Because the fruit has an unpleasant odor, it is also known as cheesy fruit or even vomit fruit.

CHEMICAL CONSTITUTION.

Noni (*Morinda citrifolia* L.) is known for manifold health benefits. Around 200 bioactive compounds were reported in Noni but their kind and concentration varies with plant parts, genotypes, environmental factors and estimation methods. Researchers isolated ninety six volatile components from Noni fruit at two different ripening stages (ripe and over ripe). Two unsaturated esters 3-methyl-3-buten-1-yl hexanoate and 3-methyl- 3-buten-1-yl octanoate significantly decreased in their concentrations in the ripe to over-ripe fruits³. Ripened fruit showed significantly higher amounts of volatile components, aldehydes, ketones, esters, alcohols, terpenes and sulphur compounds like methyl hexanoate, methyl octanoate, ethyl octanoate and methyl 4 *E*-decenoate etc, (table:1), while octanoic acid and decanoic acid concentrations were significantly lower.

Acids	Formic acid, Acetic acid, Butanoic acid, Hexanoic acid, Heptanoic acid, Octanoic acid, 2-octanoic acid, Nonanoic acid, Decanoic acid
Alcohols	Ethanol, 2-methyl-3-buten-1-ol, 1-butanol, 3-Methyl-3-buten-1-ol, 3-Methyl-2-buten-1-ol, Benzyl alcohol
Esters	Ethyl acetate, Butyl acetate, Methyl 2-methylpropanoate, Methyl butanoate, Ethyl butanoate, Butyl butanoate, Methyl 3-methylbutanoate, 4-Pentenyl butanoate, 3-Methyl-3-buten-1-yl 3-methylbutanoate, Methyl 2-methylbutanoate, Methyl hexanoate, Methyl 2-methylbutanoate, Methylhexanoate, Ethyl hexanoate, Butyl hexanoate, 4-pentanyl hexanoate, 3-Methyl-3-buten-1-yl hexanoate, Hexyl isovalerate, Methyl heptanoate, Methyl octanoate, Ethyl octanoate, Butyl octanoate, 3-Methyl-3-buten-1-yl octanoate, Methyl 2-octenoate, Methyl 3-octenoate,

	Methyl 3-octenoate, Methyl nonanate, Methyl 5-nonanate, Methyl decanoate, Ethyl decanoate, Methyl 4-decanoate, Ethyl 4-decanoate, Methyl salicylate, Methyl hexadecanoate
Terpenes	Linalool oxide, (Z)-3,7-Dimethyl-1,3,6-octatriene, (+)-4-Carene, D-Limonene, Ocimenol, Terpeneol
Sulfur Compounds	Methanethiol, S-Methyl thioacetate, Dimethyl disulfide, Methyl 3-methylthiopropionate, Ethyl 3-methylthiopropionate, 3-methylthiopropionic acid
Aldehydes and ketones	Acetaldehyde, 2-methylebutanol, 3-methylebutanal, 2-pentanone, 3-methyle-2-butanone, 2-hexanone, 2-Hexenal, Furfural, Benzaldehyde

This suggested that the presence of sulphur contributes to the flavour characteristics of Noni juice (SPME and SDE methods)⁴. It was suggested that the production process (fermentation and juice vs drying or lyophilization) has no effect on the anthraquinone content. In ripe fruit there is no as such influence on anthraquinone content. The fruit pulp contain polydatin and mature fruit contain anthraglycoside B. It has been reported that immature fruit is not ideal for therapeutic applications as only two phytochemical substances (polydatin and á-cryptoxanthin) were present (D.R. Singh *et al*, 2012)⁵. Commercial Noni products in the market whether fermented or unfermented juice or powder should be obtained from fully ripe Noni fruits and seed should be removed during drying process⁶. Compared the Total Phenolic Content (TPC) of commercial Noni juice with blueberry and grape juice, reported that Noni juice contains 65.56% of total polyphenols against 27.90% and 6.54% which represent the 5% blueberry and grape juice, respectively. Blue berry and grape juice mask the unpleasant odour and bitter taste of Noni fruit juice and allows alteration in the organoleptic properties of commercialized Noni juice. Commercial Noni juice presented higher values of TPC (91.90 mg of gallic acid/100 ml juice) and antioxidant activity (5.85 mmol/L) when compared to its 5% diluted constituents. Regarding the antioxidant activity of noni juice and its components, it was observed that 64.27 % of antioxidant activity could be represented by noni juice, and 29.40 % and 6.32 by 5 % diluted blueberry and grape juices, respectively⁷. Identified polyphenols belonging to the coumarin, flavonoid and phenolic acid groups, and two iridoids in Noni juice by HPLC-DAD and Electro Spray Ionization Mass Spectrometric detection (HPLC-ESI-MS) method.

Fermented fruit extract contain micronutrients, non-volatile and volatile components, ketones, lactones, beta-carotenoids, terpenoids, proxeronine.⁸ Physicochemical, phytochemical and antimicrobial properties of Noni fruit collected at different maturity levels were investigated. The results showed the maximum antibacterial activity in ethanolic extract of mature Noni fruit against *K. Pneumonia* (21 mm) whereas in methanolic extract of mature Noni fruit showed maximum antifungal activity against *A. Flavous* (19 mm).⁹

Mechanism of action of phytoconstituents present in various parts of Noni plant

Damnacanthal

Damnacanthal, an *anthraquinone* induced normal morphology and cytoskeletal structure in K-ras NRK cells at the tolerant temperature without changing the amount and localization of ras. The effect of damnacanthal was reversible and had not shown any effect on the morphology of RSVTs-NRK cells states the src oncogene. Hence, damnacanthal is a new inhibitor of ras function.¹⁰ The MTT method confirmed that damnacanthal inhibitor the growth of MCF-7 cells at the concentration of 8.2 µg/ml for 72 h. Moreover, damnacanthal was found to induce cell cycle (CC) arrest at the G1 check point in MCF-7 cells by CC analysis. The result provided significant evidence in demonstrating that p53-mediated damnacanthal induced apoptosis through the activation of p21 and caspase-7.¹¹

In another study, it was reported that damnacanthal acts against Hep G2 hepatocellular carcinoma cells by decreasing the phosphorylation level of Akt and targets matrix metalloproteinase-2 secretion in Hep G2 cells.¹² Reported that the damnacanthal possesses strong inhibitory activity towards tyrosine kinases i.e. Lck, Src, Lyn and EGF receptor.¹³

Epigallocatechin gallate (EGCG)

EGCG present in Noni which is known for its potent antioxidant and antiangiogenesis activity also it inhibits the quinol oxidase (NOX) enzyme, which is responsible for tumor activity. Thus, Noni helps in antiangiogenesis by inhibiting NOX.¹⁴

Alizarin and limonene

Found to inhibit the formation of blood vessels over the tumor by antiangiogenesis property. Thus Noni juice inhibit the growth and mutations of malignant cells and induce programmed cell death or apoptosis.¹⁵

Polysaccharides

Glucuronic acid, galactose, arabinose, rhamnose, glycosides and trisaccharide fatty acid ester showed immuno-stimulatory, immune-modulatory, antibacterial, antitumor and anticancer activity.¹⁶ 6-D-Glucopyranose pentaacetate is sulphated polysaccharides, which undermine the interaction between glucosaminoglycan and certain proteins. This helps to block the ability of mutated cells to adhere to new cells stopping metastasis.¹⁷

Compounds present in Noni fruit like iridoid glycosides, 6- α hydroxyadoxoside, 6 beta, 7-beta-epoxy-8-episplenoside as well as americanin, narcissoside, asperuloside, asperulosidic acid, citrifolin Bepimera, borrieriagenin, deacetylasperuloside, dehydromethoxy gaertneroside, cytidine, epi-dihydrocornin, d-glucose, d-mannitol, methyl α -d-fructofuranoside, methyl beta-d-fructofuranoside, nicotifloroside, and beta-sitosterol 3-O-beta-d-glucopyranoside showed antioxidant activity in both DPPH and NO₂ reducing activity bioassays.¹⁸ Researcher's states that Noni has good antioxidant activity, having free radical scavenging activity and quenching lipid peroxides.¹⁹

Quercetin

Reported decreased cell viability of both low metastatic cell line ACC-2 and high metastatic cell line ACC-M with quercetin treatment in a concentration and time dependent manner. Quercetin significantly decreases the apoptosis in ACC cells through a mitochondria dependent pathway which showed close correlation with down regulation of the PI3K/Akt/IKK- α /NF- κ B pathway. Their result reveals that quercetin may be a hopeful chemotherapeutic agent against ACC through its function of down regulating the PI3K/Akt/IKK- α /NF- κ B signaling pathway.²⁰

Scopoletin

Scopoletin decreases carrageen induced iNOS and COX-2 expressions in the paw edema. These anti-inflammatory mechanisms of scopoletin may be related to the reduced in the level of MDA via increasing the activities of SOD, GPx and CAT in the paw edema.²¹

Anthraquinones, saponins and scopoletin were identified by TLC techniques and their R_f value were determined.²⁷

Xeronine

Noni fruit contain proxeronine which combine with proxeroninase an enzyme present in the body to form xeronine which may help to enlarge the pore size of the tumor cells and allow

anticancer drugs to enter the cells more easily. Also, xeronine increases the permeability of K⁺ ions and prevent the formation of lactic acid from glucose.¹²

Citrifolinoside

Citrifolinoside isolated from the leaves of *M. citrifolia* plant showed significant inhibition of UVB-induced Activator Protein-1 (AP-1) activity in cell cultures.²²

Monoterpene

A monoterpene, limonene present in Noni fruit has been shown to prevent mammary, liver, lung and other cancers. Limonene stimulate thymus gland to secrete more T cells which destroy the carcinoma cells.²³

Beta carotene

Suggested that beta carotene reduced the oxygen free radical and prevent oxidative damage. Also reported that long term use of moderate dose of β -carotene significantly reduced prostate cancer incidence in male smokers.²⁴

Ursolic acid

It possess anti-carcinogenic effect both externally and internally prevent growth of cancerous cells and induce apoptosis by modulating immune process of the body.²⁵

Gallic acid

Gallic acid reduced compound 48/80-or immunoglobulin E (IgE) which induced histamine release from mast cells. The inhibitory effect of gallic acid on the histamine release was mediated by the modulation of cAMP and intracellular calcium. Gallic acid decreased the phorbol 12-myristate 13-acetate and calcium ionophore A23187-stimulated pro-inflammatory cytokine gene expression and production such as TNF- α and IL-6 in human mast cells.²⁶

BIOLOGICAL ACTIVITY

According to the European Commission 5th framework program quality of life, there are no systematic reviews or metaanalyses that have been published about the *M. citrifolia* wide ranges of therapeutical claims (Pilkington and The CAMCancer Consortium, 2015). In the next paragraph, the discussed therapeutic indications are linked to a clear scientific evidence of either in vitro and in vivo studies, or clinical trials, with a specification about the responsible phytochemical component of each activity, as well as the extracting solvent and the used part of the plant along with its country of origin.

1. Antifungal activity

Jayaraman *et al.*, has reported that the antifungal properties of Indian *M. citrifolia* fruit extract in three different solvents, methanol, ethyl acetate and hexane were tested in an in vitro assay on different fungi including *Candida albicans*, *Aspergillus niger*, *Trichophyton mentagrophytes*, *Penicillium* species, *Fusarium* species, *Aspergillus fumigates*, *Rhizopus* species, *Aspergillus flavus*, and *Mucor* species. The maximum inhibition was in the methanol and ethyl acetate extract of 79.3% and 62.06%, respectively against *Trichophyton mentagrophytes*, while almost 50% inhibition was recorded in the methanol extract against *Penicillium*, *Fusarium* and *Rhizopus* species, and none of the extracts were active against either *Candida albicans* or *Aspergillus* species²⁸. Despite the fact that in vitro results for anti-bacterial and anti-fungal studies are promising yet further in vivo and clinical research are highly recommended using different routes of administrations.

2. Antioxidant activity

Australian *M. citrifolia* fruit juice showed an anti-oxidant activity 2.8 and 1.4 times higher than vitamin C and pycnogenol, respectively. This antioxidant activity was similar to grape seed powder at the daily dose recommended by U.S.RDAs and manufacturers²⁹. Neolignan and americanin A were the potent antioxidant constituent of the American *M. citrifolia* fruit³⁰ (Su et al., 2005). The optimum magnitudes of radical scavenging activity (RSA), and total phenolic content of Malaysian seedless *M. citrifolia* fruit methanol extract were 55.60% and 43.18 mg GAE/10 g, respectively³¹. In other study, *M. citrifolia* anti-oxidant activity was evaluated as a natural antipigmentation agent by observing the effect of 50% ethanol extracts of Tahitian *M. citrifolia* fruit flesh, leaves, and seeds, on the tyrosinase enzyme responsible for controlling the production of melanin. The in vitro test was carried out using tyrosinase inhibitory assay, showing that seed extract had stronger tyrosinase inhibitory (from 20 to 500 lg/ml) and antioxidant activity than the fruit (500 lg/ml), while leaf extract did not have any tyrosinase inhibitory activity at any concentration. The tyrosinase inhibitory activity was linked to the presence of lignans in *M. citrifolia*, particularly 3,30-bis demethylpinoresinol and americanin A³². The same seed extract was found to have anti-photoaging activity at concentrations ranging from 0.5 to 1.0 mg/ml³³ and also inhibited blood hemagglutination at concentrations ranging from 50 to 500 lg/ml³⁴. Ursolic acid was the responsible chemical for the both activities. *M. citrifolia* anti-oxidant property was also linked to other health enhancements activities. In an in vitro evaluation of methanol, chloroform, ethanol, butanol and aqueous extract of Indonesian *M. citrifolia* fruit, all extracts were able to inhibit Low-density lipoprotein (LDL) oxidation due to *M. citrifolia* lignans, such as americanol A, americanin A, americanoic acid A, morindolin, and isoprincepin³⁵. Other in vitro study suggested Malaysian *M. citrifolia* leaf ethanol extract was a highly effective natural anti-obesity supplement than its fruit. Leaf and fruit methanol extracts inhibited the lipoprotein lipase activity $66\% \pm 2.1$ and $54.5\% \pm 2.5\%$, respectively. Both extracts contain high levels of phenolic constituents including catechin, epicatechin and rutin which acted synergistically to demonstrate this activity³⁶. Furthermore, Tahitian *M. citrifolia* juice was able to reduce obesity related to insulin resistance in an in vitro mouse muscle cells C2C12 culture, by inhibiting the reactive oxygen species and mitochondrial damage³⁷. A clinical study was carried out on twenty-two participants (16 women and 6 men), aged between 18 and 65 years old for 12 weeks trial of a weight-loss program with a fixed study factors including Tahitian *M. citrifolia* -based dietary supplements (US brand), daily calorie reduction, and exercise. All participants experienced weight loss with significant decrease in fat mass without side effects. However, the researchers suggested that further clinical studies should be carried out to include more male participants, and ethnic diversity³⁸. Antidyslipidemia activity was related to *M. citrifolia* antioxidant property in the aqueous-ethanol extracts of its Indian fruits, leaves, and roots in Sprague–Dawley rats and mice of either sex, all these different parts extracts caused significant reduction in total cholesterol, triglyceride (TC), low density lipoprotein-cholesterol, atherogenic index and TC/HDL ratio. There were no behavioral changes, toxicity or mortality occurred up to 10 g/kg of *M. citrifolia* intake, as compared to control group³⁹. Hepato-protective effects *M. citrifolia* was also affined to anti-oxidant effects in its Taiwanese fermented fruit juice at a dose range of 3–9 mL NJ/kg BW on hamsters fed with a high-fat diet⁴⁰.

3. Anti-inflammatory activity

In an in vitro study, the anti-inflammatory activity was detected in the Costa Rican *M. citrifolia* fruit juice by measuring its direct inhibitory activities on cyclooxygenase (COX)-1 and -2⁴¹. The in vivo study on Tahitian *M. citrifolia* fruit juice showed a reduction in the induced carrageenan paw edema in rats, revealing a strong anti-inflammatory effect

comparable to that of non-steroidal inflammatory drugs, such as acetylsalicylic acid, indomethacin and celecoxib, without side effects⁴². Tahitian *M. citrifolia* seeds oil showed topical anti-inflammatory activity by inhibiting both COX-2 and 5-LOX enzymes in an in vitro assay at concentrations of 0.5 and 1 mg/ml⁴³. The topical safety of the *M. citrifolia* seed oil was evaluated on 49 adult volunteers using the patch test whereas topical comedogenic effect of the seed oil was studied on 23 Caucasian adolescent volunteers. Both studies were conducted for four weeks, and results indicated that the topical *M. citrifolia* seed oil was safe and non-comedogenic, in addition to showing a very little risk of causing allergic dermatitis which could be due to seed high fatty acids content, mainly linoleic acid⁴³.

A randomized double-blind placebo-controlled trial using a *M. citrifolia* dietary supplement (U.S brand) was first performed on 100 women above 18 years old, however, only 80 women completed the study. The aim of the study was to find out the potential natural anti-inflammatory efficacy of *M. citrifolia*. This study included some variables such as age, parity, body mass index, pain, menstrual blood loss, hemoglobin, packed cell volume and erythrocyte sedimentation rate before and after treatment. Patients were observed for three menstrual cycles after being exposed to 400 mg of *M. citrifolia* capsules or placebo (38 in the placebo group and 42 in the *M. citrifolia* group) and there were no significant differences in any of the variables studied between treated and placebo group, further studies using higher doses of *M. citrifolia* with a larger sample size were recommended⁴⁴ (Fletcher et al., 2013).

4. Cardiovascular activity

Noni fruit preventing arteriosclerosis, a disease related to the oxidation of low density lipoproteins (LDL). This beneficial effect could be due to the presence of lignans, phenylpropanoid dimers⁴⁵ (Kamiya et al., 2004).

5. Anti-arthritis activity

An Indian brand of *M. citrifolia* fruit juice was orally administered to arthritic rats at doses 1.8 ml/kg and 3.6 ml/kg, and showed a dose dependent significant reduction in paw thickness, arthritic index, secondary lesions, mononuclear infiltration and pannus formation. Similar changes were also recorded by the administration of indomethacin except for the reduction of secondary lesions. The anti-arthritis activity could be due to the presence of flavonoids and phenols⁴⁶ (Saraswathi et al., 2012). Precise investigations can add a therapeutic value by specifying the chemicals owning such activities and their effective and safe doses.

6. Anti-cancer activity

M. citrifolia natural components are mostly reported as a natural anticancer cure where sulphated polysaccharide stops metastasis by destabilizing the interaction between glycosaminoglycan and certain proteins⁴⁷ (Liu et al., 2000) while damnacanthol inhibits the formation of tumors either by interfering with the growth of ras gene activation⁴⁸ (Hiramatsu et al., 1993), or by increasing apoptosis in human colorectal cancer cell lines⁴⁹ (Nualsanit et al., 2012). Alizarin has an antiangiogenic effect through blocking blood circulation to malignant tumors. Limonene prevents mammary, liver, and lung cancers by stimulating thymus gland to secrete more T cells which destroys the carcinoma cells. Last but not the least, ursolic acid inhibits the growth of cancerous cells and induces apoptosis by modulating the body immune process⁵⁰ (Lv et al., 2011).

7. Antidiabetic activity

Indian *M. citrifolia* commercial fruit juice was administered orally to induced steroid diabetic (diabetes type 2) female Wistar rats, at a dose of 1.8 and 3.6 ml/kg for 10 days. The blood

glucose level was significantly decreased compared to control induced diabetic rats by dexamethasone. At higher oral dose (3.6 ml/kg, twice a day) *M. citrifolia* fruit juice had better results than rosiglitazone, but caused liver damage in rats⁵¹(Puranik et al., 2013). On the other hand, fermented juice of South American *M. citrifolia* also controlled blood sugar induced diabetic rats by streptozotocin. Diabetic standard animals, treated with hypoglycemic drug, glibenclamide, while diabetic experimental animals treated with 2 ml/kg *M. citrifolia* twice a day for 20 days exhibited a significant reduction in blood glucose level of 125 mg/dl and 150 mg/dl, respectively, as compared to untreated diabetic rats with fasting blood sugar of 360.0 mg/dl⁵² (Shivananda Nayak et al., 2011). Hypoglycemic activity of Tahitian *M. citrifolia* fruit Juice was investigated by administering the juice to male Sprague–Dawley rats at a dose of 1 ml/150 g body weight, twice daily for 4 weeks prior to diabetic induction using alloxan. After induction, a rise in blood glucose levels occurred but followed by a steady decline due to *M. citrifolia* juice prophylaxis against the diabetogenic agent, alloxan⁵³(Horsfal et al., 2008).

CONCLUSION

The Great Morinda - *Morinda citrifolia* has a wide range of activity. The noni fruit juice has a high demand in the market and it is used as an alternative medicine for various kinds of diseases. Many phytochemicals were identified from different parts of the plant, among all these parts, noni fruit shows the high range of phytochemicals and activity such as anti-cancer, anti-oxidant, anti-inflammatory, analgesic, anti-diabetic, anti-microbial. The most important compounds identified in noni fruits are damnacanthal and scopoletin (phenolic compounds), compound named xeronine(alkaloid), caproic and caprylic acid (organic acids), ascorbic acid and provitamin A, aspartic acid, and minerals. Although many studies are done, more studies need to ensure the true potential of noni fruits.

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